

PHARMACOLOGY SECTION
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α -BENZYL-TETRAHYDROFURFURYLAMINES—
A NEW SERIES OF PSYCHOMOTOR STIMULANTS

III. THE PHARMACOLOGY OF D-THREO
 α -BENZYL-N-ETHYL-TETRAHYDROFURFURYLAMINE
(ZYLOFURAMINE) (1)

BY

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ALLES (1933) first pointed out the central nervous system (CNS) stimulatory properties of β -phenylisopropylamine, amphetamine. Since that time, a large number of phenylethylamine derivatives have been found to have CNS activity and some of these have become useful therapeutic agents (BROWN and WERNER, 1954; MEIER, *et al.*, 1954; DRILL 1958).

Recently some α -benzyltetrahydrofurfurylamines have been prepared which, like amphetamine, are characterized by their ability to stimulate the spontaneous activity of mice and rats (CLARKE and HARRIS, 1962). The members of this series have two asymmetric centers and thus can exist in *dl-threo* and *dl-erythro* forms which, in several instances, have been isolated. In the case of α -benzyl-N-ethyltetrahydrofurfurylamine, resolution of each of the racemates was accomplished to afford all four optical isomers (CLARKE, *et al.*, 1962). Assessment of the psychomotor stimulatory properties of these four isomers revealed that the *d-threo* form, zylofuramine, Fig. 1, was the most potent. This compound has been submitted to an extensive pharmacological study which is the basis of the present report.

(1) Presented in part at the meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 14, 1962.

METHODS

Spontaneous activity.

The effect of zylofuramine on the spontaneous activity of mice was assessed in activity cage and activity wheel studies. Activity cage studies were carried out by a modification (HARRIS and UHLE, 1961) of the photocell technique of DEWS (1953). The apparatus consisted of a round metal box sixteen inches in diameter with a wire mesh bottom and a lucite top. A beam of light passing across one diameter impinged on a photoelectric cell so adjusted that a mouse breaking the light path activated a magnetic digital counter.

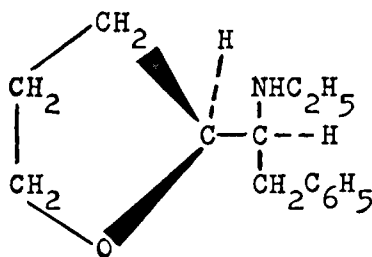


FIG. 1

Male albino mice ⁽¹⁾ (18–20 g) were used once only. They were allowed free access to food and water until placed in the activity cage.

The drugs, dissolved in distilled water, were given orally. All dosages were expressed in terms of drug base. Groups of five mice were medicated, placed in the activity cage, and given ten minutes in which to adjust to the environment. The apparatus was then turned on and the number of interruptions of the light beam was recorded for a thirty minute period. Eight to twelve groups of mice were run at each dose level. Control groups receiving distilled water were run concurrently.

Activity wheel studies were carried out using standard wheels. ⁽²⁾ Single mice were medicated orally and placed in the wheel; recording was begun immediately. Revolutions were recorded electronically and were read at forty-five minute intervals for three hours. The activity wheels were housed in a soundproofed, constant temperature room and the counters were remotely located. Controls were run daily.

⁽¹⁾ All mice used in this study were a Swiss-Webster strain obtained from Albany Farms, Altamont, New York.

⁽²⁾ George H. Wahmann Co., Baltimore, Maryland.

Overt behavior.

The effect of zylofuramine on the overt behavior of cats and monkeys was assessed by direct observation. All observations were carried out by a single trained person. The normal behavior patterns of each animal were obtained by observation over a period of several weeks. Changes produced by the drugs in this normal pattern of behavior were assessed using a simple rating scale.

- ++ marked increase
- + some increase
- o no change
- some decrease
- — marked decrease

The parameters of behavior examined were: general activity, excitability, grooming, and aggressiveness.

Cardiovascular studies.

Cats and dogs were anesthetized with Dial-Urethane ® (1) and prepared for the polygraphic recording of blood pressure and lead II electrocardiogram. Blood pressure was obtained from the carotid artery through a Statham pressure transducer. The drugs, dissolved in saline, were administered via a polyethylene catheter inserted in the femoral vein. In some cases bilateral vagotomy was performed prior to drug administration.

To ascertain the cardiovascular effect, zylofuramine was administered to dogs trained to lie quietly on their sides for long periods of time. Blood pressure was taken from the foreleg using a child's blood pressure cuff. Heart rate was recorded by stethoscope.

Electroencephalographic studies.

The effect of zylofuramine on electrocortical activity was determined in unanesthetized, unrestrained cats bearing implanted cortical electrodes. The cats were prepared in a manner similar to that described by BRADLEY and ELKES (1953). The Teflon-covered, 0.055-inch stainless steel wires were inserted, under sterile conditions, through stereotaxically located burr holes in the skull. The wires were fixed in place with acrylic dental cement and led out, through a stab wound in the neck, to a subminiature connector. Bilateral electrodes were placed in frontal (posterior sigmoid), occipital (middle suprasylvain), and parietal (post-

(1) Kindly supplied by Dr. A. J. PLUMMER, Ciba Pharmaceutical Products, Inc.

erior lateral gyri) areas. A heavier stainless steel wire, used to anchor the other wires to the sagittal crest, was utilized as an indifferent electrode.

All surgery was performed under Pentabrocanol® anesthesia and the cats were given a course of antibiotic therapy (10,000 units potassium penicillin G, 10,000 units Depo-Penicillin® and 20 mg tetracycline) for three days following surgery. The animals were allowed two to four weeks for recovery before drugs were administered. While recovering, the cats were periodically placed in an observation box in a soundproofed constant temperature room. During these adaptation sessions EEG tracings and the normal behavior pattern of the animals were obtained.

On medication days the cats were placed in the box and the EEG and behavior were followed for one hour. At this time, either saline or the drug was administered intraperitoneally, the cat placed back in the box, and observation and recording continued for another three to six hours. No cat was medicated more than once a week.

Antiappetite studies.

A colony of cats was maintained whose health and eating habits had been stabilized over a long period of time. These cats were arranged in groups of five, and the mean food intake per day per cat was determined for each group over the three days prior to medication. The drugs, dissolved in distilled water, were administered by stomach tube and the mean food intake per day was determined for the three days following medication. Control groups receiving distilled water were run concurrently.

Acute toxicity.

Groups of ten male mice (18–23 g) were medicated with logarithmically increasing doses of the compound, placed in wire mesh cages, and the number dead at twenty-four hours and seven days was determined. The percent dead (7 days) was plotted against log-dose on probit paper and the LD₅₀ and its standard error were determined by the method of MILLER and TAINTER (1944).

For the aggregated toxicity studies both the grouped (10 animals) and single animals were housed in identical 10 × 7 × 7 inch galvanized metal cages with wire mesh floor and front. Room temperature was kept constant at 72° F and no compensation was made for the decreasing population of the aggregated groups due to deaths.

Body temperature.

Male white mice (not fasted) weighing 18–23 g were used. The

temperature was observed by means of a rectal thermometer recording from a galvanometer (Tele-Thermometer, Yellow Springs Instrument Co., Inc.). Groups of 20 animals were medicated orally with zylofuramine (10.0 mg/kg) and *d*-amphetamine (10.0 mg/kg) immediately after control temperature readings were obtained. The temperatures were again noted 1 and 2 hours later.

RESULTS

The results of the photocell activity cage study are shown in Fig. 2.

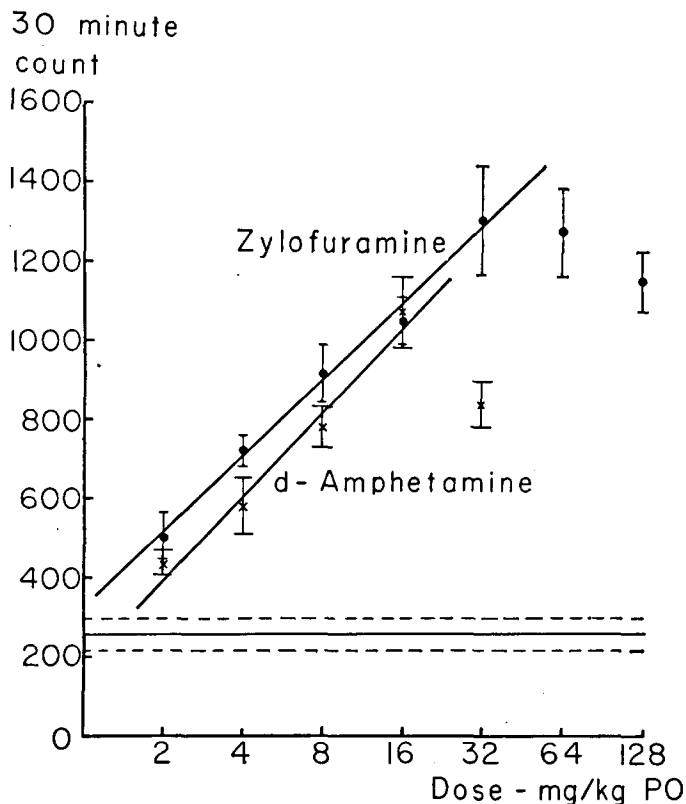


FIG. 2

Comparative effects of zylofuramine and *d*-amphetamine on the spontaneous activity of mice. Photocell activity cage. Each point and bar represents the mean $\pm$ the standard error from eight groups of five mice. The mean control and its standard error are shown as horizontal lines.

Zylofuramine was somewhat more potent than *d*-amphetamine in its ability to stimulate the spontaneous activity of mice. The threshold

oral dose for significant stimulation was 2.0 mg/kg for both amines. Zyloruramine produced a higher degree of stimulation than did *d*-amphetamine at most doses and the doses response curves were approximately parallel. The sharp drop in activity usually seen with high doses of amphetamine was not as apparent with the furfururamine.

Zyloruramine was also able to reverse the depression of activity produced in mice by chlorpromazine. The intraperitoneal administration of 3.0 mg/kg of chlorpromazine produced an 80 % reduction in spontaneous activity. This depression was completely reversed or blocked by the oral administration of 4.0 mg/kg of zyloruramine. Similarly, EDWARDS (1962) reported the prevention of catalepsy induced by chlorpromazine in rats.

The results of the activity-wheel studies (TABLE I) paralleled those obtained in the photocell experiment. Comparable doses of zyloruramine, in mice, produced a greater degree of running activity than did *d*-amphetamine. In general, it was difficult to find a dose of *d*-amphetamine which produced a good, consistent increase in running in these wheels.

TABLE I

The effect of zyloruramine and d-amphetamine on the running activity of mice in activity wheels

Drug	Dose mg/kg	Number of Revolutions			
		0-45 mins.	45-90 mins.	90-135 mins.	135-180 mins.
H ₂ O	—	285	208	158	91
<i>d</i> -Amphetamine	3.0	175*	205	200	183*
	6.0	362*	300*	289*	238**
	12.0	218	191	164	225**
Zyloruramine	3.0	358*	360*	273*	213*
	6.0	393*	462**	349**	293**
	12.0	400*	463**	413**	384**

* Significant difference from controls at $p < 0.05$.

** Significant difference from controls at $p < 0.01$.
(Student's *t*-test).

Overt behavior studies in cats and monkeys also indicated that zyloruramine was an active CNS stimulant, about one-fourth as potent

as *d*-amphetamine. However, good stimulation was observed with zyloramine over a wider dose range (2.0–32.0 mg/kg p.o.) in both species. An increase in the amount of grooming was noted at low doses and a marked increase in general activity and excitability was seen at higher doses. There was no change in aggressiveness with either compound. The differences between the two compounds were more striking in the monkey where amphetamine stimulates only over a narrow dose range (0.5–2.0 mg/kg) and is quite toxic. The marked salivation, mydriasis, and hyperexcitability seen with amphetamine was not observed with the furfurylamine except at lethal doses.

The effects of zyloramine on the cardiovascular system were very mild. In anesthetized dogs and cats, even large initial doses produced only a small, transient pressor response (TABLE II). There was a concomitant decrease in heart rate in animals with intact vagi and a slight increase in rate in vagotomized animals. Tachyphylaxis was observed with frequently repeated doses. With increasing doses, the pressor response was converted to a depressor response. There appeared to be an enhancement of the pressor response to levarterenol after treatment with the furfurylamine.

TABLE II

Comparative effects of zyloramine and d-amphetamine on the blood pressure of anesthetized dogs

Drug	Dose mg/kg i.v.	Average Peak Pressor Response* mm Hg
Zyloramine	1.25	no effect
	2.5	11/6
	5.0	14/10
<i>d</i> -Amphetamine	0.31	18/17
	0.62	59/22
	1.25	54/43

* Mean values from 3 dogs at each dose.

The results of crossover experiments comparing zyloramine and *d*-amphetamine in anesthetized, vagotomized dogs are shown in Table III. As can be seen, 0.1 mg/kg of *d*-amphetamine produced a greater pressor

response than 1.0 mg/kg of zylofuramine. On crossover second administrations one hour later the pressor response to zylofuramine was slightly greater and that of *d*-amphetamine slightly less. These differences were not statistically significant. Similar results were obtained in anesthetized cats.

TABLE III

Crossover study comparing single doses of zylofuramine and d-amphetamine in anesthetized, vagotomized dogs

First Injection			Second Injection		
Drug	Dose mg/kg i.v.	Mean Pressor Response mm Hg*	Drug	Dose mg/kg i.v.	Mean Pressor Response mm Hg*
Zylofuramine	1.0	0	<i>d</i> -Amphetamine	0.1	27
<i>d</i> -Amphetamine	0.1	35	Zylofuramine	1.0	11

* Mean values from 5 dogs at each dose.

In unanesthetized dogs, oral doses of 2.5 and 5.0 mg/kg of zylofuramine produced only a small pressor response. There was a slight increase in heart rate with the lower dose and a slight decrease in rate with the higher dose. *d*-Amphetamine, at much smaller doses, (0.3 and 0.6 mg/kg) produced a marked increase in both systolic and diastolic pressure. These changes were accompanied by a decrease in heart rate. Thus, zylofuramine appears to be considerably less than one-tenth as active as *d*-amphetamine on the cardiovascular system.

Electroencephalographic studies in cats with zylofuramine revealed that small doses (0.5 and 1.0 mg/kg) produced electrographic alerting which was often unaccompanied by observable behavioral changes. Higher doses (2.0 to 8.0 mg/kg) produced behavioral as well as electrographic alerting. The results of a typical experiment are illustrated in Fig. 3. Normally, animals in this situation display a quiet, drowsy behavior which is reflected in the electrocorticogram. Twelve minutes after the administration of zylofuramine, the predominant pattern of high voltage slow activity was nearly completely replaced by low voltage fast activity. This electrically alert state persisted for a long period and was accompanied, in this experiment, by behavioral changes only during

the first half-hour. This sustained electrocortical arousal could readily be counteracted by chlorpromazine. In its effects on the electrocortical activity of cats, zylufuramine was found to be about one-half as potent as *d*-amphetamine.

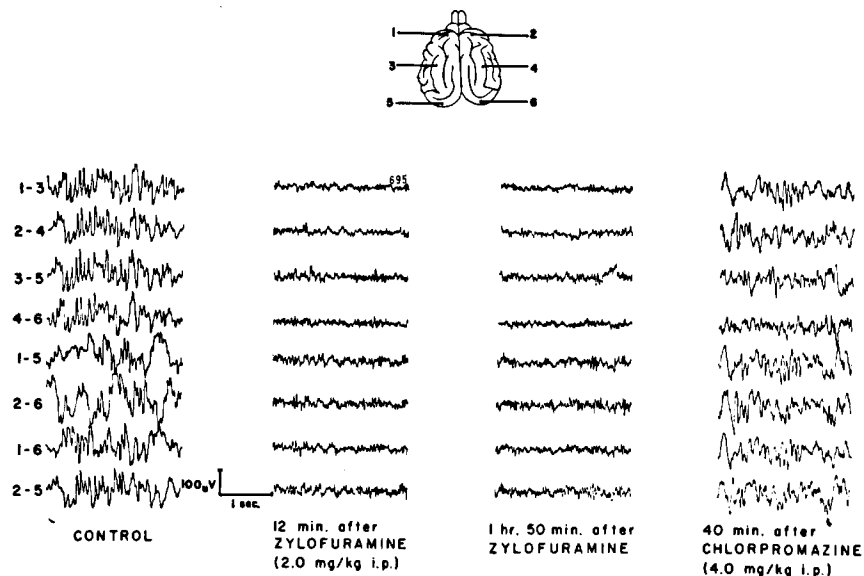


FIG. 3

Effect of zylufuramine on the electrocortical activity of the unanesthetized cat.

Antiappetite studies in cats indicated that zylufuramine was less than one-eighth as active as *d*-amphetamine. An oral dose of 8.0 mg/kg of the furfurylamine was required to produce a significant decrease in food intake. A greater depression of appetite was obtained with 1.0 mg/kg of *d*-amphetamine.

The acute toxicity values for zylufuramine and *dl*-amphetamine by the oral and the intravenous routes are shown in Table IV. These data indicate that the furfurylamine is about one-third to one-fifth as toxic as *dl*-amphetamine. ⁽¹⁾

GUNN and GURD (1940) observed that amphetamine was considerably more stimulatory to crowded animals than it was to solitary animals. CHANCE (1946), and later LASAGNA and MCCANN (1957), reported that amphetamine was several times more toxic to aggregated mice than to single animals. It was of interest, therefore, to ascertain whether zylufuramine produced the same effect. The results of this study are shown

⁽¹⁾ The authors are indebted to Mr. Leon DUPREY for these data.

TABLE IV
Acute toxicity studies in mice

Drug	Route of Administration	LD ₅₀ mg/kg $\pm$ S.E.
Zylofuramine	i.v.	32 $\pm$ 2
	p.o.	475 $\pm$ 66
<i>dl</i> -Amphetamine	i.v.	15 $\pm$ 4
	p.o.	90 $\pm$ 23

in Table V. The usual five-fold increase in the toxicity of *d*-amphetamine was observed, but this difference was not seen with the furfurylamine. There was considerably less hyperexcitability and autonomic stimulation noted in the animals medicated with zulofuramine.

The comparison of the effects of zylofuramine and *d*-amphetamine on body temperature is shown in Table VI. Zylofuramine had no effect on body temperature, while *d*-amphetamine produced a significant ($P < 0.05$) hyperthermia. Again, there appeared to be an equivalent degree of stimulation in both groups, although the salivation, pilo-erection and other autonomic signs were absent in the furfurylamine treated animals.

TABLE V
The effect of aggregation on the acute toxicity of zylofuramine and d-amphetamine in mice

Compound	Subcutaneous LD ₅₀ mg/kg $\pm$ S.E.	
	Single	Crowded
Zylofuramine	170 $\pm$ 28	155 $\pm$ 39
<i>d</i> -Amphetamine	110 $\pm$ 6	20 $\pm$ 10

A number of auxiliary studies were carried out with the furfurylamine. The compound was not a monoamine oxidase inhibitor nor did it block β -hydroxylase, the enzyme system responsible for the conversion of

dihydroxyphenylethylamine to nor-epinephrine. The blood glucose levels of normal, fasted rats were unchanged following administration of large doses of the compound.

TABLE VI

The effect of zylofuramine and d-amphetamine on the rectal temperature of mice

Time	Temperature — °C ± S.E.	
	Zylofuramine 10.0 mg/kg p.o.	d-Amphetamine 10.0 mg/kg p.o.
0'	37.7 ± 0.39	37.6 ± 0.50
60'	37.7 ± 0.44	38.2 ± 0.72
120'	37.5 ± 0.48	*38.9 ± 0.51

* Significant at the $p < 0.05$ level.
(Student's *t*-test).

DISCUSSION

The high stimulating potency of zylofuramine in mice is noteworthy. Tainter and his colleagues (SCHULTE *et al.*, 1941; TAINTER, 1943; NOVELLI and TAINTER, 1943), in a study of nearly one-hundred phenylalkylamines, found only one compound, methamphetamine, which was more potent than *d*-amphetamine. The tetrahydrofurfuryl portion of the molecule appears to endow it with a high degree of specificity since the unsaturated furfuryl compounds and a number of simple alkyl ethers have little stimulatory activity (CLARKE and HARRIS, 1962). The high level of stimulation, the lack of hyperexcitability, and the absence of marked autonomic stimulation are also of interest. Indeed, the ability of the compound to produce and maintain a marked elevation of locomotor activity, as compared to *d*-amphetamine, might be related to this inability to over-excite. The poor results obtained with *d*-amphetamine in the activity wheels could be related to the smaller degree of stimulation produced by this agent in isolated as compared to grouped animals (GUNN and GURD, 1940). The difficulties encountered by others with this method are well known (RILEY and SPINKS, 1958). Zylofuramine is

also highly effective in reversing the depression of spontaneous activity produced by chlorpromazine. This is true in single as well as grouped mice.

The effect of zylofuramine on the overt behavior of cats and monkeys confirms the results seen in rodents. The compound is stimulatory over a wide dose range and does not produce the hyperexcitability, autonomic stimulation, and toxicity which is seen with amphetamine. Some social behavior studies were also carried out using grouped monkeys. Neither zylofuramine nor *d*-amphetamine effected a definite change in the social or "peck" order of these grouped animals. It was thought that the low ranked animals treated with the furfurylamine showed an increase in courage and attempted activities (eating, drinking, swinging on the trapeeze, etc.) before satiation of the "lead" animals. There was, however, no displacement of the lead animals in the overall social order.

Zylofuramine, like pipradrol (BROWN and WERNER, 1954), has little effect on appetite. It has been noted (MODELL, 1960; FRIEDMAN, 1960) that, among the sympathomimetic anorexogenic agents, there is a good correlation between anorexogenic activity and central stimulation. However, many potent central stimulants (methylphenidate, pentyl-enetetrazol, picrotoxin, pipradrol, etc.) have little or no effect on appetite.

The cardiovascular effects of zylofuramine were unremarkable. It was of interest that no dose of this compound was able to provoke the intensity of cardiovascular response produced by amphetamine. If the cardiovascular effects of amphetamine can be accounted for on the basis of the hypothesis of BURN and RAND (1958), then zylofuramine is a much less effective liberator of endogenous amines.

In the electroencephalographic studies it was felt that electrocortical arousal without concomitant behavioral signs could be obtained more readily with zylofuramine than with *d*-amphetamine. Some attempt was made to find the locus of action of zylofuramine utilizing techniques similar to those employed by BRADLEY and ELKES (1957) in studying amphetamine. In two *encéphale isolé* experiments zylofuramine eliminated all spindle and slow activity. In three *cerveau isolé* experiments large doses (8.0–16.0 mg/kg i.v.) of the compound converted the high voltage slow activity to a low voltage fast pattern. Spindling did not reappear for periods of up to one hour. This would indicate that mesencephalic connections are not entirely necessary for this drug to exert an effect on electrocortical activity. Whether zylofuramine, like amphetamine, also has a direct effect on the reticular formation (KILLAM, 1962) is currently under investigation.

The increased toxicity displayed by amphetamine on aggregation of the test animals has been attributed to increased excitement (BURN and HOBBS, 1958), anxiety or fear (SWINYARD *et al.*, 1961), or to motor activity and increased body temperature (GREENBLATT and OSTERBERG, 1961). Zylfuramine, while it caused an equivalent degree of psychomotor stimulation, did not show increased toxicity on aggregation. On the other hand, *d*-amphetamine produced an increase in body temperature which was not seen with the furfurylamine. This would indicate that hyperthermia plays some role in the phenomenon of increased toxicity on crowding, as the data of HÖHN and LASAGNA (1960) would indicate.

A clinical evaluation of this compound is now in progress and the details of these studies will be published at a later date.

SUMMARY

Some pharmacological properties of *d*-*threo*- α -benzyl-N-ethyltetrahydrofurfurylamine, zylfuramine, have been described. Zylfuramine was found to be more potent than *d*-amphetamine as a psychomotor stimulant in mice and readily reversed the depression produced by chlorpromazine. The stimulation produced by this furfurylamine was unaccompanied by the autonomic stimulation and hyperexcitability seen with amphetamine. Overt behavior studies in cats and monkeys revealed that zylfuramine was somewhat less potent than *d*-amphetamine but was active over a wider dose range. Electrocortical and behavioral arousal was seen in unanesthetized, unrestrained cats with intraperitoneal doses of 2.0 to 8.0 mg/kg. Electrocortical alerting alone was often seen at 0.5 and 1.0 mg/kg.

Zylfuramine showed little cardiovascular activity in anesthetized dogs and cats and in unanesthetized dogs. The compound appeared to be considerably less than 1/10 as active as *d*-amphetamine in this regard. Zylfuramine had little effect on appetite and did not block the monoamine oxidase or β -hydroxylase enzyme systems.

Zylfuramine was found to have relatively low acute toxicity and did not display an increase in toxicity on aggregation. This finding was attributed, in part, to the finding that zylfuramine did not produce an increase in body temperature.

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